Development of small molecule screens for autism using patient-derived iPS cells

Grant Award Details

Development of small molecule screens for autism using patient-derived iPS cells

Grant Type: Tools and Technologies II

Grant Number: RT2-01906

Project Objective: The objective of this project is to develop and validate a drug screening platform using iPSC-derived neurons from patients with autism spectrum disorders (ASD) to identify new therapies for ASD.

Investigator:

Name:	Theo Palmer
Institution:	Stanford University
Type:	PI

Disease Focus: Autism, Neurological Disorders, Pediatrics

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,797,606

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Development of small molecule screens for autism using patient-derived iPS cells

Public Abstract:

Autism Spectrum Disorders (ASDs) are a heritable group of neuro-developmental disorders characterized by language impairments, difficulties in social integrations, and the presence of stereotyped and repetitive behaviors. There are no treatments for ASDs, and very few targets for drug development. Recent evidence suggests that some types of ASDs are caused by defects in calcium signaling during development of the nervous system. We have identified cellular defects in neurons derived from induced pluripotent stem cells (iPSCs) from patients with Timothy Syndrome (TS), caused by a rare mutation in a calcium channel that leads to autism. We propose to use cells carrying this mutant calcium channel to identify drugs that act on calcium signaling pathways that are involved in ASDs.

Our research project has three aims. First, we will determine whether known channel modulators reverse the cellular defects we observe in cells from TS patients. It is possible that we will find that existing drugs already approved for use in humans might be effective for treating this rare but devastating disorder.

Our second aim is to determine whether screens using neuronal cells derived from ASD patients can be used to identify calcium signaling modulators. A bottleneck to therapy development for ASDs has been the lack of appropriate in vitro models for these disorders, and we would like to determine whether our studies could serve as the basis for a new type of screen in human neurons.

Our third aim is to identify signaling molecules that might be affected in patients with ASDs, which could be targets for future drug discovery. There is increasing evidence that several types of ASDs are caused by defects in neuronal activity and calcium signaling. More specifically, the CaV1.2 calcium channel that we are studying has been implicated in syndromic and non-syndromic forms of autism, and also in schizophrenia and bipolar disorder. One of the more exciting aspects of our screen of neurons with a mutation in CaV1.2 is that it gives us a tool to explore calcium-mediated signaling pathways that are defective in ASDs. We will try to modify calcium signaling in neurons from ASD patients by changing the expression of proteins that are known to affect calcium signaling in other contexts. These experiments will identify targets that are active in human neurons and that affect cellular phenotypes that are defective in ASD.

In summary, the work described in this proposal constitutes a critical step to fulfilling the promise that reprogramming of patient-specific cells offers for the treatment of neuropsychiatric disorders such as autism. Our studies will identify lead compounds that could be tested in the clinic for a rare form of autism, and novel molecular targets for therapeutic development in the future. Importantly, these studies will provide a proof of principle that iPSC-derived cells are valuable for drug discovery for neuropsychiatric disorders.

Statement of Benefit to California:	Autism Spectrum Disorders (ASDs) affect approximately 1 in 110 children in California. In addition to the devastating effects that ASDs have on the families of affected individuals, treating and educating people with ASDs imposes a heavy economic burden on the state. In 2007, almost 35,000 individuals with autism were receiving services from the California Regional Centers, and the number was expected to rise to 50,000 by last year. Recent estimates suggest that the lifetime cost of caring for an individual with an ASD can exceed $3 million. In spite of their impact on our society, there are currently no effective therapies for ASDs. Our lack of cellular and molecular tools to study these disorders means that there are no good targets for drug screening, so there are very limited prospects for developing effective pharmacological treatments in the near future. New drug discovery paradigms are needed to help develop therapies for these neuropsychiatric conditions. The research described in this proposal could have a dramatic impact on drug discovery methods for ASDs. First, we hope to identify drugs that are effective in treating Timothy Syndrome, a rare form of autism caused by an electrophysiological defect in a calcium channel. Second, we aim to develop new tools to explore calcium-mediated signaling pathways that are defective in ASDs. If successful, our research will identify a family of molecular targets that will be useful for developing therapies for ASDs in the future.